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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-364/SE8-016

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA #:	20-364
SERIAL #:	SE8-016
DRUG NAME:	Lotrel (amlodipine and benazeprile HCl)
INDICATION:	Treatment of hypertension
APPLICANT:	Novartis
DOCUMENTS REVIEWED:	Volumes 1, 10, and 11 of 41, dated 6/ 29/01
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FreidlinV/Lotrel/20364_r1/01-11-02

TABLE OF CONTENTS

EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

The sponsor submitted results of a single Study 104 to assess efficacy and safety of a higher dosage strength of Lotrel in the treatment of hypertension. Since this NDA contains only one clinical study, the EXECUTIVE SUMMARY OF STATISTICAL FINDINGS is identical to SUMMARY AND REVIEWER'S CONCLUSIONS at the end of this document.

OVERVEW OF DESIGN OF STUDY 104

The sponsor submitted results of a Phase 4, single Study 104 to assess efficacy and safety of a new, higher dosage strength of Lotrel, which combines 10 mg of amlodipine and 20 mg of benazepril HCl in the treatment of hypertension. A currently marketed formulation of Lotrel is a combination capsule containing amlodipine 5 mg and benazepril 20 mg for oral administration in the treatment of patients with hypertension. In this review, abbreviations Lotrel 10/20 and Lotrel 5/20 are used instead of Lotrel (amlodipine 10 mg/benazepril 20 mg) and Lotrel (amlodipine 5 mg/ benazepril 20 mg), respectively.

Study 104 was a double-blind, randomized, 3-arm, placebo-controlled, forced-titration, parallel-group, multicenter trial in patients with essential hypertension. Patients were randomized to receive either Lotrel 5/10 mg or placebo for 2 weeks. Those patients receiving Lotrel 5/10 mg were titrated to either Lotrel 5/20 mg or Lotrel 10/20 mg for 6 weeks. Patients receiving placebo remained on placebo for additional 6 weeks.

The objective of Study 104 was to compare the safety and efficacy of new product Lotrel 10/20 mg once daily to a marketed product Lotrel 5/20 mg once daily, and placebo once daily in patients with essential hypertension.

EFFICACY AND SAFETY VARIABLES

Primary efficacy variable

The primary efficacy variable was change from baseline in mean sitting diastolic blood pressure (MSDBP). At all visits, blood pressure was to be taken three times in the sitting position. Initial measurements were to be taken after the patient had been in the sitting position for 5 minutes. Repeat measurements were to be made at 1 to 2-minute intervals.

Secondary efficacy variable

The secondary efficacy variable was change from baseline in mean sitting systolic blood pressure (MSSBP).

Safety

At each visit during the trial, after Visit 1, all new or continuing adverse experiences (AEs), which were not present at the initial visit (Visit 1) were recorded. Any medical condition present at the initial visit, which remained unchanged or improved, was not recorded as an AE at subsequent visits.

SPONSOR'S STATISTICAL METHODS

Primary efficacy population was the ITT population. The primary time point was Endpoint. For each patient and variable, the Endpoint measurement was defined as the patient's last post-baseline measurement of either Visit 4 or 5 of that variable carried forward. The ITT population included all randomized patients who had a baseline (Visit 2) measurement and at least one post-baseline measurement of either Visits 4 (Week 4) or Visit 5 (Week 8).

Secondary efficacy population was all randomized patients at Visit 5 (Week 8). This set consisted of all randomized patients who have both a baseline (Visit 2) measurement and a Visit 5 measurement.

Criteria for efficacy

Lotrel 10/20 was considered more effective than Lotrel 5/20 in lowering the blood pressure of essential hypertensive patients if Lotrel 10/20 has a statistically significant greater reduction from baseline in MSDBP compared to Lotrel 5/20.

The Lotrel 10/20 treatment or the Lotrel 5/20 treatment is considered effective in lowering the blood pressure of essential hypertensive patients if Lotrel 10/20 treatment or Lotrel 5/20 treatment had a statistically significant greater reduction from baseline in MSDBP compared to the placebo group, respectively.

For each patient, a successful response in the control of MSDBP is defined as a MSDBP < 90 mm Hg or a ≥ 10 mm Hg decrease from baseline.

Each variable was analyzed using a two-way analysis of covariance (ANCOVA) model with treatment and trial center as factors and baseline (pre-dose measurement at the randomization visit)

as a covariate. Both treatment-by-center and treatment-by-baseline interactions were included in the model. The hypotheses tested were as follows:

Primary Hypothesis

The treatment effect of Lotrel 10/20 was equal to the treatment effect of Lotrel 5/20 versus they were not equal.

Secondary Hypotheses

The treatment effect of Lotrel10/20 was equal to the treatment effect of placebo versus they were not equal. The treatment effect of Lotrel 5/20 was equal to the treatment effect of placebo versus they were not equal.

For each of the comparisons as defined above, the test was two-sided at the significance level ≤ 0.05.

Pooling of centers for ANCOVA

To avoid potential analysis problems in the ANCOVA due to small centers (e.g., no patients in a center for some treatment groups), the following pooling algorithm was used. The objective of the algorithm was to minimize the amount of pooling and still avoid problems that can occur with too few patients per treatment group in any pooled center. Pooling was performed so that, for the analysis of the primary efficacy variable (change from baseline in MSDBP), at least three randomized patients (with analysis measurements) were available per treatment group in all pooled centers at all analysis time points. After eliminating individual centers, which meet these criteria on their own, the remaining centers were pooled. Pooling was performed after first sorting the remaining individual centers by (a) the total number of patients per center available for analysis (using the minimum overall evaluation time points) and then by (b) the center numbers (1, 2, 3, ...) previously assigned at trial initiation. Beginning with the largest and progressing to the smallest, these centers were pooled sequentially by sorting order, until the required pooling criteria were met. If the last set of centers did not fulfill the pooling requirements, then those centers were pooled with the last set of pooled centers which did meet the requirements. Pooling began with the larger centers to be pooled and progressed to the smaller ones to avoid the case in which the last set of pooled centers could result in a comparatively large pooled center.

For variables other than the primary efficacy variable, pooling was identical to that for the primary efficacy variable as long as the distribution of patients across trial centers for these other variables was equal to or greater than that for the primary efficacy variable. The need for more extensive pooling for variables with fewer numbers of patients per treatment-center cell was evaluated prior to data analysis and, if needed, used the same pooling algorithm described above. Pooled center was used as a factor in the ANCOVA analyses instead of the actual center. Response at each time point was analyzed using logistic regression with treatment group as a factor and the results presented as point estimates with 95% confidence intervals. The primary efficacy variable was change from baseline in MSDBP. The secondary efficacy variable was change from baseline in MSSBP. The change from baseline in sitting pulse was also evaluated. The evaluation of safety is based on all randomized patients who have at least one post safety measurement. Proportions of patients with adverse event were compared by this reviewer with the Fisher's exact test. No interim analyses were planned or performed.

Sample size

A total of 300 patients (100 per treatment group) who meet all admission/randomization criteria and complete all visits of the double-blind period of the trial were targeted for this protocol. The sample size calculations were based on the primary efficacy variable: change from baseline in mean sitting diastolic blood pressure (MSDBP).

The sample size was calculated to have statistical power of ≥ 80% for rejecting the two-sided null hypothesis at the 0.05 significance level, when the alternative hypothesis is true. The unknown true difference in MSDBP was assumed to be at least 3.0 mm Hg between Lotrel 10/20 and Lotrel 5/20, with a standard deviation of 7.5 mm Hg.

REVIEWER'S STATISTICAL METHODS

In agreement with the medical reviewer, this reviewer accepted the study design and analysis plan used by the sponsor with the following exceptions. The sponsor's efficacy comparisons of the three treatment arms were performed at the 0.05 alpha level (without alpha correction for multiplicity). Since no criterion for multiple comparison adjustment was given in the protocol, this reviewer used the Bonferroni correction for multiple comparisons of the three treatment arms to maintain Type 1 error at the 0.05 level. That is, primary efficacy pairwise comparisons in this review were performed at the 0.0167 level of alpha.

This reviewer compared the baseline balance among treatment groups relative to age (<65 years vs. ≥65 years), gender, race, and presence of past significant medical history based on all randomized patients. Treatment group baseline comparability was examined using a chi-square test. The chi-square test was also used to compare the safety profiles of the three treatment groups and proportions of dropouts in different analysis populations.

RESULTS OF STUDY 104

PATIENT DISPOSITION

A summary of patient discontinuation by treatment group and study period is provided in Table 1. Of the 457 patients enrolled in this study, 386 (84.5%) were randomized (Visit 2). The majority (74.6%; 53 of 71) of patient discontinuations prior to randomization were due to an abnormal lab value or failure to meet protocol criteria.

Of the 457 enrolled patients, 349 (76.4%) patients were titrated at Visit 3 (Week 2). The discontinuation profile during the period between randomization and titration was similar among those patients who had received Lotrel 5/20 mg or Lotrel 10/20 mg with one exception. The number of patients who discontinued due to an abnormal lab value was higher among patients who received Lotrel 10/20 mg compared to patients who had received Lotrel 5/20 mg (4 patients vs. 1 patient). Of the patients who discontinued prior to titration, approximately half (51.3%; 19 of 37) had received placebo (p=0.055). The number of patients who discontinued due to an unsatisfactory therapeutic effect or failure to meet protocol criteria was noticeably higher among placebo patients than those who received either Lotrel 5/20 mg or Lotrel 10/20 mg.

Table 1. Patient disposition by period and treatment					
		Lotrel 5/20	**Lotrel 10/20**	**Placebo**	**P[¶] value**
Number of patients					
Placebo run-in	Visit 1 (Total=457)				
Randomization[†]	Visit 2 (Week 0) (Total=386)	127	125	134	
Titration *	Visit 3 (Week 2) (Total 349)	120 (94%)	114 (91%)	115 (86%)	0.055
Completed study,	Visit 4 or 5 (Total=328)	114 (90%)	108 (86%)	106 (79%)	0.049
Patients who discontinued prematurely pre-titration					
Total = 37		7 (6%)	11 (9%)	19 (14%)	0.055
Patients who discontinued post-titration					
Total = 21		6 (5%)	6 (5%)	9 (7%)	0.62
†: Patients received Lotrel 5/10 mg or placebo					
*Dose titrated to Lotrel 5/20 mg or Lotrel 10/20 mg.					

[¶] Reviewer's analysis.

Of the 457 enrolled patients, 328 (71.8%) patients completed this study. There was a marginally statistically significant difference (p=0.049) between the treatment groups relative to the number of patients who completed the study with more discontinuations in the placebo group. Five patients in the placebo group discontinued post titration due to an unsatisfactory therapeutic effect, while no patients in either Lotrel group discontinued due to an unsatisfactory therapeutic effect.

ANALYSIS POPULATIONS

Primary efficacy population included all randomized patients at Endpoint. This primary data set contained all randomized patients who had a baseline (Visit 2) measurement and at least one post-baseline measurement at either Visit 4 or Visit 5. The Endpoint was defined as the last post-baseline measurement obtained at either Visit 4 or Visit 5. Of the 386 randomized patients, a total of 348 (90%) patients had at least one post-baseline value at Visit 4 or Visit 5: 114 received Lotrel 10/20 mg, 119 received Lotrel 5/20 mg, and 115 received placebo (p=0.094).

Secondary efficacy population included all randomized patients at Visit 5 (Week 8). This set contained all randomized patients who had a baseline (Visit 2) measurement and a Visit 5 measurement. Of the 386 randomized patients, a total of 334 (87%) patients met this criterion for inclusion: 109 received Lotrel 10/20 mg, 116 received Lotrel 5/20 mg, and 109 received placebo (p=0.058).

Safety Population included those who were randomized and had at least one post baseline safety measurement. Of the 386 patients randomized (127 Lotrel 5/20 mg patients, 125 Lotrel 10/20 mg patients, and 134 placebo patients), 384 (99%) were included in the analysis of safety.

Baseline demographic and background characteristics

Overall, the majority of patients were white (65.3%), less than 65 years of age (77.7%), had a significant medical history (92.2%), and had taken antihypertensive medication within the 3 months preceding study enrollment (78.8 %). The demography and medical history were similar for the three treatment groups at baseline. There was no statistically significant difference between the treatment groups at baseline relative to gender (p= 0.22), race (p= 0.94), age group (p= 0.053), or significant medical history (p= 0.33).

EFFICACY RESULTS

A decrease in MSDBP from baseline (Visit 2) to Endpoint and to Visit 5 is shown in Table 2. The mean change from baseline to Endpoint for patients who received Lotrel 10/20 mg, Lotrel 5/20 mg, and placebo groups was -15.7 mm Hg, -14.8 mm Hg, and -5.4 mm Hg, respectively (Table 2).

Table 2. Change from baseline (Visit 2) to Endpoint and Visit 5 in MSDBP (mm Hg) by treatment group[¶]

	Primary Efficacy analysis. Endpoint			Secondary efficacy analysis. Visit 5		
Treatment	Base	Post	Change	Base	Post	Change
Lotrel 10/20						
N	114	114	114	109	109	109
Mean	100.5	84.8	**-15.7**	100.5	84.5	-16.0
S.D.	4.5	8.1	7.2	4.5	7.9	6.9
Lotrel 5/20						
N	119	119	119	116	116	116
Mean	100.3	85.6	**-14.8**	100.3	85.6	-14.7
S.D.	4.5	8.5	7.6	4.5	8.6	7.6
Placebo						
N	115	115	115	109	109	109
Mean	101.2	95.8	-5.4	101.1	95.4	-5.6
S.D.	4.5	9.6	8.0	4.5	9.7	8.1

[¶] Sponsor's analysis.

The primary efficacy analysis showed that Lotrel 10/20 mg was only numerically more effective than Lotrel 5/20 mg relative to reduction in MSDBP from baseline to Endpoint. When the two Lotrel treatment groups were compared, difference in reduction in MSDBP was not statistically significant ($p = 0.19$; Table 3). Compared to the placebo group, a statistically greater reduction in MSDBP from baseline to Endpoint was observed in patients who received either Lotrel treatment ($p < 0.0001$; Table 3).

Table 3. Change from baseline (Visit 2) in mean sitting diastolic blood pressure (mm Hg) at Endpoint and Visit 5[¶]

Comparison	Time	Least square estimate	p[¶]-value	95% confidence interval
Lotrel 10/20 vs. Lotrel 5/20	**Endpoint**	**-1.3776**	**0.19**	**(-3.44, 0.68)**
	Visit 5	-1.8073	0.088	(-3.88, 0.27)
Lotrel 10/20 vs. placebo	Endpoint	-10.5224	< 0.0001	(-12.58, -8.47)
	Visit 5	-10.6530	<0.0001	(-12.75, -8.56)
Lotrel 5/20 vs. placebo	Endpoint	-9.1448	<0.0001	(-11.18, -7.11)
	Visit 5	-8.8458	<0.0001	(-10.92, -6.77)

[¶] Sponsor's analysis.

Secondary efficacy analysis showed a similar pattern for the change in MSDBP from baseline to Visit 5. Lotrel 10/20 mg was not statistically significantly more effective than Lotrel 5/20 mg relative to the reduction in MSDBP from baseline to Visit 5 ($p = 0.088$; Table 3). Secondary efficacy analysis showed that a significantly greater reduction in MSDBP from baseline to Visit 5 occurred in patients who received either Lotrel dosage compared to placebo ($p < 0.0001$; Table 3).

In this study, a successful response in the control of MSDBP was defined as a MSDBP < 90 mm Hg or a ≥ 10 mm Hg decrease in MSDBP. At Endpoint, 87.7% of patients who received Lotrel 10/20 mg, 79.8% of patients who received Lotrel 5/20 mg, and 32.2% of placebo patients achieved a successful response in the control of MSDBP (Table 4). The difference between the Lotrel treatment groups was not statistically significant ($p = 0.11$, Table 4). There was a statistically significant difference in the percentage of patients who had a successful response between either of the Lotrel treatment groups and placebo group ($p < 0.0001$, Table 4).

At visit 5, the percentage of patients who responded successfully in the control of MSDBP for patients receiving Lotrel 10/20 mg or placebo was greater than at Endpoint (89.0% vs. 87.7% and 33.0% vs. 32.2%, respectively, Table 4). The percentage of patients who responded successfully was significantly greater in the Lotrel treatment groups compared to placebo ($p < 0.0001$, Table 44).

Table 4. Percent of patients who achieved a successful response in the control of MSDBP (mm Hg) at Endpoint and Visit 5 [¶].

Comparison		Treatment 1		Treatment 2		
(treatment 1 vs. treatment 2)	Time	n/N	%	n/N	%	p-value
Lotrel 10/20 vs. Lotrel 5/20	Endpoint	100/114	87.7	95/119	79.8	0.12
	Visit 5	97/109	89.0	92/116	79.3	0.068
Lotrel 10/20 vs. placebo	Endpoint	100/114	87.7	37/115	32.2	< 0.0001
	Visit 5	97/109	89.0	36/109	33.0	< 0.0001
Lotrel 5/20 vs. placebo	Endpoint	95/119	79.8	37/115	32.2	< 0.0001
	Visit 5	92/116	79.3	36/109	33.0	< 0.0001

A successful response was defined as a mean sitting diastolic blood pressure < 90 mm Hg
Or a ≥ 10 mm Hg decrease compared to baseline.
N denotes number of patients with successful response.
N denotes number of patients evaluated.

[¶] Sponsor's analysis.

Table 5. Change from baseline (Visit 2) to Endpoint and Visit 5 in MSSBP (mm Hg)

	Endpoint			Visit 5		
Treatment	Base	Post	Change	Base	Post	Change
Lotrel 10/20						
N	114	114	114	109	109	109
Mean	155.7	133.6	-22.1	155.9	133.2	-22.7
S.D.	14.7	12.5	14.1	15.0	12.1	13.8
Lotrel 5/20						
N	119	119	119	116	116	116
Mean	153.2	132.8	-20.4	153.0	132.8	-20.3
S.D.	14.5	14.8	12.6	14.5	14.9	12.7
Placebo						
N	115	115	115	109	109	109
Mean	152.0	147.4	-4.6	151.3	146.8	-4.6
S.D.	15.0	14.0	12.3	15.1	14.0	12.5

Table 6. Change from baseline (Visit 2) in MSSBP (mm Hg) at Endpoint and Visit 5¶				
Comparison	**Time**	**Least square estimate**	**p-value**	**95% confidence interval**
Lotrel 10/20 vs. Lotrel 5/20	Endpoint	-1.2448	0.43	(-4.34, 1.85)
	Visit 5	-1.5564	0.33	(-4.69, 1.57)
Lotrel 10/20 vs. placebo	Endpoint	-16.3115	< 0.0001	(-19.41, -13.21)
	Visit 5	-16.1927	< 0.0001	(-19.38, -13.01)
Lotrel 5/20 vs. placebo	Endpoint	-15.0667	< 0.0001	(-18.13, -12.00)
	Visit 5	-14.6363	< 0.0001	(-17.77, -11.50)

¶ Sponsor's analysis.

At visit 5, the difference in successful response between Lotrel treatment groups was not statistically significant (p = 0.068, Table 4).

Decrease in mean sitting systolic blood pressure (MSSBP) from baseline (Visit 2) to Endpoint and Visit 5 is presented in Table 5. The mean change for patients in the Lotrel 10/20 mg, Lotrel 5/20 mg, and placebo groups was -22.1 mm Hg, -20.4 mm Hg, and -4.6 mm Hg, respectively (Table 5). The reduction in MSSBP when Lotrel treatment groups were compared was not statistically significant (p = 0.43, Table 6). A statistically significantly greater reduction occurred in Lotrel treatment groups compared to placebo (p < 0.0001, Table 6).

EFFICACY SUBGROUP ANALYSIS

Study 104 was not powered for the subgroup analysis. For all patient sub-populations examined, the mean change in MSDBP from baseline to Endpoint was numerically greater among patients who received Lotrel (either dose) than placebo patients, and greater for patients who received Lotrel 10/20 mg compared Lotrel 5/20 mg. When Lotrel treatment groups were compared, the difference in the change from baseline to Endpoint was numerically greater among patients ≥ 65 years of age (2.2 mm Hg) compared to < 65 years of age (0.7 mm Hg). This was similar for female patients who had a greater change from baseline (1.4 mm Hg) than male patients (1.0 mm Hg). This was also similar for black patients (2.6 mm Hg) compared to white patients (0.2 mm Hg) or an "other" race (1.7 mm Hg).

SAFETY RESULTS

Adverse experiences were summarized for all randomized patients who had at least one post-baseline safety measurement. Adverse experiences included events that occurred during the pre-titration and post-titration periods. Table 7 presents the number and percentage of patients with

adverse experiences by body system and treatment group. The profile of adverse events was similar for patients who received Lotrel 5/20 mg, Lotrel 10/20 mg, or placebo. The difference between the treatment groups was not statistically significant for all body systems ($p \geq 0.05$) except for metabolic and nutritional disorders ($p=0.035$).

The percentage of patients who had at least one adverse experience was similar within each group: 62.2% of patients who received Lotrel 5/20 mg, 61.6% of patients who received Lotrel 10/20 mg, and 60.6% of placebo patients ($p=0.97$). Slightly more patients in the Lotrel 10/20 group (26.4%) experienced events related to study medication compared to the Lotrel 5/20 (22.8%) or placebo (22.0%), with $p=0.68$.

Table 7. Number of randomized patients with AEs by treatment and body system

	Lotrel 5/20		Lotrel 10/20		Placebo	
Body system	N	%	N	%	N	%
Total number of patients	127		125		132	
Number of patients with an AE	79	62.20	77	61.60	80	60.61
Body as a whole	22	17.32	27	21.60	24	18.18
Cardiovascular system	2	1.57	5	4.00	4	3.03
Digestive system	12	9.45	21	16.80	18	13.64
Hemic and lymphatic system	3	2.36	0	0.00	2	1.52
Metabolic and nutritional disorder*	3	2.36	0	0.00	0	0.00
Musculoskeletal system	20	15.75	16	12.80	18	13.64
Nervous system	26	20.47	31	24.80	33	25.00
Respiratory system	31	24.41	23	18.40	25	18.94
Skin and appendages	12	9.45	9	7.20	8	6.06
Special senses	8	6.30	3	2.40	4	3.03
Urogenital system	7	5.51	7	5.60	4	3.03
Laboratory abnormality	0	0.00	2	1.60	2	1.52
Surgical and medical procedure	3	2.36	4	3.20	3	2.27
Infections and infestations	6	4.72	6	4.80	5	3.79

* Statistically significant difference ($p=0.035$)[¶].

[¶] Reviewer' analysis.

SUMMARY AND REVIEWER'S CONCLUSIONS

The sponsor submitted results of a Phase 4, single Study 104 to assess efficacy and safety of a new, higher dosage strength of Lotrel, which combines 10 mg of amlodipine and 20 mg of benazepril HCl in the treatment of hypertension. A currently marketed formulation of Lotrel is a combination capsule containing amlodipine 5 mg and benazepril 20 mg for oral administration in the treatment of patients with hypertension. In this review, abbreviations Lotrel 10/20 and Lotrel 5/20 are used instead of Lotrel (amlodipine 10 mg/benazepril 20 mg) and Lotrel (amlodipine 5 mg/ benazepril 20 mg), respectively.

Study 104 was a randomized, double-blind, 3-arm, multicenter trial to compare the safety and efficacy of the new product Lotrel 10/20 mg once daily to a marketed product Lotrel 5/20 mg once daily, and placebo once daily in the treatment of patients with essential hypertension. The primary efficacy variable was change from baseline to Endpoint in mean sitting diastolic blood pressure (MSDBP). The secondary efficacy variable was change from baseline in mean sitting systolic blood pressure (MSSBP). In the sponsor's analysis, primary efficacy comparisons of the three treatment arms were performed at the significance level of 0.05 (without correction for multiplicity). Since no criterion for multiple comparison adjustment was given in the protocol, this reviewer used the Bonferroni correction for multiple comparisons of the three treatment arms to maintain Type 1 error at the 0.05 level.

The ITT population of Study 104 included 114 patients in the Lotrel 10/20 group, 119 patients in the Lotrel 5/20 group, and 115 patients in the placebo group. Primary efficacy analysis showed that the difference in the MSDBP reduction from baseline to Endpoint between Lotrel 10/20 mg and Lotrel 5/20 mg was equal to 0.9 mm Hg and was not statistically significant ($p = 0.19$). Compared to the placebo group, both the Lotrel 10/20 group and Lotrel 5/20 group had statistically significantly greater reduction from baseline ($p < 0.0001$) both in MSDBP and MSSBP. Results in the secondary efficacy population supported the results in the ITT population. Safety profiles of patients in the three treatment groups were similar. There were no statistically significant differences between the treatment groups relative to the proportions of patients with adverse experiences by body system except for metabolic and nutritional disorders ($p=0.035$).

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